INCREASED RETINAL OXYGEN SUPPLY FOLLOWING PAN-RETINAL PHOTOCOAGULATION AND VITRECTOMY AND LENSECTOMY*

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PANRETINAL PHOTOCOAGULATION AND VITRECTOMY ARE WIDELY USED IN THE treatment of proliferative diabetic retinopathy. Both treatments seem to beneficially affect the progress of retinal neovascularization, although the mechanism of this effect is not well understood. However, hypoxia in the retina is commonly blamed for proliferative retinopathies[1,2] and a treatment which would alleviate the retinal hypoxia might beneficially affect the retinopathy.

We have investigated the effect of panretinal photocoagulation on the oxygen supply to the inner retina and also the effect of combined lensectomy and vitrectomy on the oxygenation in the eye. We conclude that both panretinal photocoagulation and vitrectomy/lensectomy increase the oxygen supply to the inner retina.

Panretinal photocoagulation increases the oxygen flux from the choroid to the inner retina. In the case of vitrectomy and lensectomy, the flow of relatively oxygen rich aqueous along the inner surface of the retina seems to provide the inner retina with additional oxygen. Vitrectomy and lensectomy reduce the oxygen tension in the aqueous humor in the anterior chamber.

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MATERIALS AND METHODS

PANRETINAL PHOTOCOAGULATION

A. *Laser Treatment*

Eight rhesus monkeys (Macaca Mulatta) were anesthetized with intramuscular ketamine hydrochloride 20-30 mg/kg (Ketaset R) and 0.05 mg/kg atropine sulfate. A retrobulbar injection of 3 ml 1% lidocaine and hylaluronidase (Wyeth^{R}), was given prior to photocoagulation. The monkey was placed on a platform in front of the slit lamp to which the argon laser (Coherent Radiation) was attached. An assistant held the monkey's head while the surgeon directed the laser beam into the monkey's eye through a hand held flat corneal contact lens with methylcellulose (Goniosol^{R}) filling the space between the contact lens and the monkey's cornea. All laser applications were done by the same surgeon (MBL) and in the same way as human patients are treated. The laser intensity was just enough to produce a white spot in the retina where applied. The exposure time was 0.2 seconds, the power 70-150 milliwatts and the spot diameter usually 500 μ, but 200 μ and 100 μ spots were also used. Three hundred to 500 burn spots were produced on either the superior or the inferior half of the fundus. Fundus photographs were taken of the monkey eye before and after the laser treatment (Fig 1).

B. *Stabilizing the Retinal Circulation - Theory*

In order to evaluate the oxygenation of the retina it is necessary to stabilize in some way the variable input of the retinal circulation. If left intact, the retinal circulation will autoregulate its resistance and blood flow and mask changes in oxygen supply (or demand) to the extent of its regulatory capacity. In some earlier experiments[3,4,5] we occluded the retinal circulation by pressing a probe on the optic disc, occluding all retinal circulation and thus eliminating this variable input on retinal oxygenation. However, occluding the retinal vessels not only keeps oxygen away from the inner retina, it also starves the inner retina of other nutrients and prevents removal of waste products.

We have developed a new procedure to stabilize the oxygen contribution from the retinal circulation in the experimental situation. The method takes advantage of the very high blood flow through the choroid and the fact that the choroidal oxygen tension can be raised close to the arterial PO_2 when the animal is breathing pure oxygen at one atmosphere pressure. When the oxygen tension in the inner retina is affected by an oxygen flux from the choroid and is raised above the saturation PO_2 of hemoglobin, the hemoglobin in the retinal circulation enters and leaves

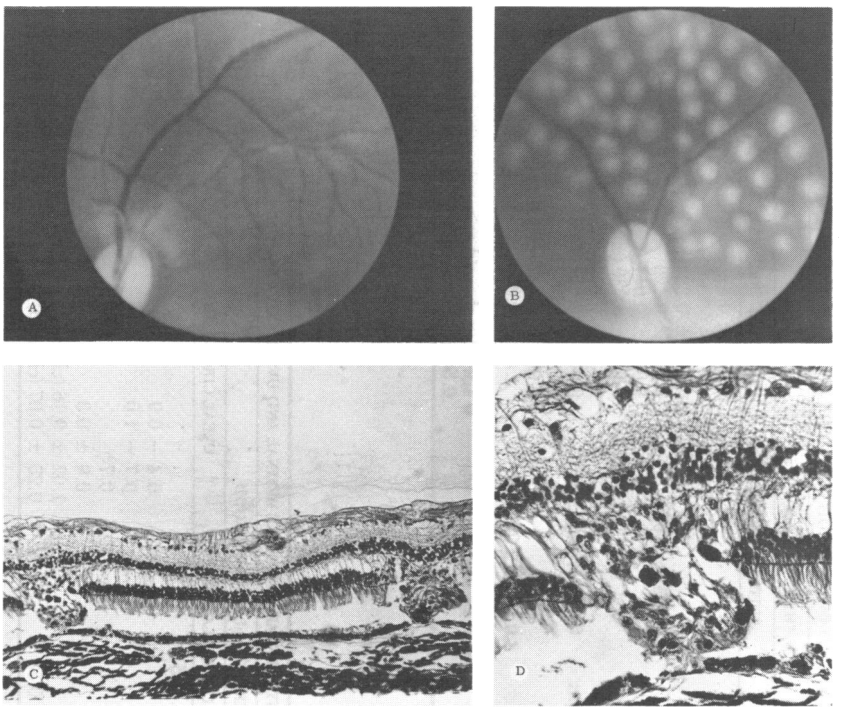


FIGURE 1

A: Rhesus monkey fundus prior to photocoagulation. B: Rhesus monkey fundus after scattered photocoagulation of the superior half of the fundus. Spot size 500 μ, power 0.1-0.15 mW, exposure time 0.2 sec. Argon laser. C: Histology of laser lesion in rhesus monkey retina showing two photocoagulation lesions. Photocoagulation lesion involves the outer retina and pigment epithelium and leaves the inner retina and the choroid almost intact (H & E, X40). D: Laser lesion in higher magnification. Note that the lesion involves mainly the outer retina. (H & E, X100).

the retinal circulation fully saturated with oxygen. In this situation the retinal circulation is almost completely ineffective in supplying oxygen and changes in the retinal blood flow do not affect the oxygen tension in the inner retina. The oxygen tension of the inner retina will depend on the oxygen flux coming from the choroid and the amount of oxygen consumed in the outer retina.

The rate of the flow in the choroid is very high (Table I)[6,7,8] and normally in the choroidal circulation less than 4% of the oxygen is lost from the hemoglobin during transit[9,10] (Table II). Alm and Bill[11,12] found the blood flow through the choroid in cats to be 734 mg/min and the A-V

TABLE I: RETINAL AND UVEAL BLOOD FLOW

BLOODFLOW IN THE EYE (ml/min)				
REFERENCE	METHOD	ANIMAL	RETINAL CIRCULATION	UVEAL CIRCULATION
8	Direct (cannulation)	Cat		1.20 ± 0.41
10	Direct	Cat		1.14 ± 0.23
12	Microspheres	Cat	0.015 ± 0.002	1.070 ± 0.122 0.060 ± 0.011 (iris) 0.262 ± 0.030 (ciliary body) 0.734 ± 0.094 (choroid)
15, 16	Microspheres	Macaca Irus	0.034 ± 0.002	0.008 ± 0.001 (iris) 0.081 ± 0.006 (ciliary body) 0.677 ± 0.067 (choroid)
7	Microspheres	Macaca Mulatta	0.05 ± 0.04	1.44 ± 0.38
62	85 Kr Clearance	Cat	0.17 (0.09 − 0.28)	1.2 ml/g choroid min
66	N_2O Dilution	Dog		0.56 ml/g uvea min

TABLE II: ARTERIOVENOUS OXYGEN CONTENT DIFFERENCE IN THE RETINAL AND UVEAL CIRCULATION

A-V O_2 DIFFERENCE ml O_2/100 ml BLOOD			
INVESTIGATOR	ANIMAL	RETINAL CIRCULATION	UVEAL CIRCULATION
19, 64	Man	Approx. 7.5	
9	Dog		0.4 − 0.9
65	Dog		0.7 − 1.0
63	Dog		0.7
67	Dog		0.9 ± 0.3
10	Cat		1.02 ± 0.16 (choroid ~ 0.08)
68	Pig	4.82 ± 0.58	0.25 ± 0.07 (choroid)

O_2 difference about 0.8 vol% making the oxygen extraction 5.6 µl O_2/min out of which 5.3 µl are supplied to the outer retina. They suggest the O_2 extraction from the retinal circulation to be 1.4 µl O_2/min. Sendroy et al[13] found the O_2 solubility in whole blood to be 0.0230 ml O_2 ml^{-1} atm^{-1} (hemoglobin bound oxygen not counted). The choroidal circulation in the cat can carry 16.9 µl O_2 min^{-1} atm^{-1} in the dissolved state. If the A-V PO_2 difference in the choroidal circulation is 0.4 atm (300 mm Hg) the choroidal blood will supply the cat retina fully and release 6.7 µl O_2 min^{-1} of oxygen that was dissolved in the blood.

We have been able to demonstrate that after the retinal circulation has been occluded the total oxygen requirements of the cat retina can be supplied by the chorio-capillaris alone when the cat breathes 60%-100%T O_2 at one atmosphere.[3,14]. This indicates that the flow rate in the choroid is so high that the oxygen dissolved in the blood makes a significant contribution to the oxygen transport and indeed can supply the oxygen requirements of the surrounding tissue under hyperoxic conditions at normal atmospheric pressure.[3,14]

Alm and Bill[15,16] used radioactive microspheres to estimate the rate of ocular blood flow in cynomologus and vervet monkeys. They found the choroidal blood flow to be 600-700 mg/ml, whereas the retinal blood flow was 25-34 mg/ml (Table I). O'Day et al[7] used microspheres to measure the ocular blood flow in the rhesus monkey and found that the choroidal blood flow was 1.4 ± 0.5 ml/min and the retinal blood flow 0.05 ± 0.04 ml/min (Table I). From O'Day's measurements, the calculated amount of oxygen in the dissolved state (hemoglobin bound oxygen not counted) in the choroidal circulation in the rhesus monkey is 32 µl O_2 min^{-1} atm^{-1}. The choroidal circulation in the cat or monkey breathing 100% O_2 can carry and release much more dissolved oxygen than is used by the retina and choroid (Table III). Information is not available on the oxygen consumption of the rhesus monkey retina, but judging from the results of this study, it is similar to other mammalian retinas (Table III).

When the monkey is breathing pure oxygen, the choroidal PO_2 rises to very high levels[3,14] and the oxygen flux from the choroid to the retina is increased and reaches the inner retina and vitreous. If this O_2 flux raises the inner retinal PO_2 above the saturation PO_2 of hemoglobin, then hemoglobin will enter and leave the retinal circulation fully saturated and the retinal circulation will contribute practically nothing to the oxygenation of the tissue. Due to the relatively low rate of blood flow the amount of oxygen released from serum in the retinal circulation is a small part of the O_2 consumption of the tissue even if the animal is breathing pure O_2. In high oxygen tension, the retinal circulation is constricted[17,18,19] and

TABLE III: RETINAL O_2 CONSUMPTION MEASURED IN VITRO

REFERENCE	ANIMAL	BUFFER SOLUTION	Q_{O_2} (ml O_2/g dry wt/hr)	CALCULATED O_2 CONSUMPTION* ml O_2 / 100 g min
69	Rat	Bicarbonate	30.7	10.2
70	Rat	Bicarbonate	20.3	6.8
		Phosphate	24.5	8.2
71	Rat	Bicarbonate	32	10.2
		Phosphate	17.5	5.8
72	Rat	Bicarbonate	31 ± 2.3	10.3
		Phosphate	18.4 ± 0.6	6.1
73	Rat	Bicarbonate	26 ± 1.5	8.7
74	Cattle	Bicarbonate	6.4 – 16.2	2.1 – 5.4
75	Cattle	Phosphate	10.6 ± 0.4	3.5
		+ Glucose	9.8 – 12.8	3.3 – 4.3
		Various add.	8.0 – 14.9	2.7 – 5.0
76	Cattle	Tris, bicarbonate or phosphate	7.42 ± 0.84	2.5
		+ Glucose	11.35 ± 1.38	3.8
		+ Succinate	14.39 ± 1.35	4.8
77	Rat	Phosphate and bicarbonate	Approx. 0.5	0.2
	Frog	Bicarbonate	Approx. 4.0	1.3
78	Frog	Bicarbonate	0.84 ± 0.02 (dark)	0.28
			0.36 ± 0.02 (light)	0.12

*(approx: dry/wet = 0.2)

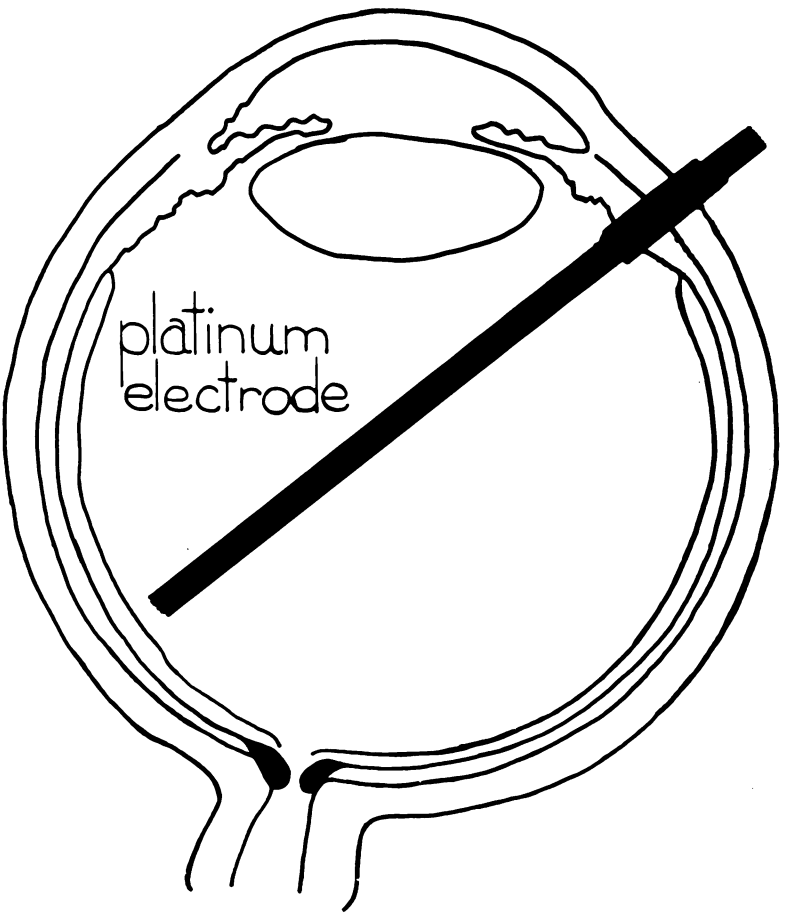


FIGURE 2
Schematic drawing of an eye with an oxygen electrode in the vitreous close to the retina. This corresponds to the experimental situation where the preretinal oxygen tension is measured and the oxygen supply to the retina from the choroid is evaluated.

the blood flow reduced below normal. With the retinal circulation not delivering a significant amount of oxygen, we have the retina supplied at the outer border by a constant pressure oxygen source (ie, the choroid) and we can measure the oxygen tension on the inner border of the retina (in the preretinal vitreous) with an oxygen electrode (Fig 2, 3). Fick's[20] law of diffusion predicts that the oxygen tension fall across the retina is a linear function of the oxygen consumption of the tissue.

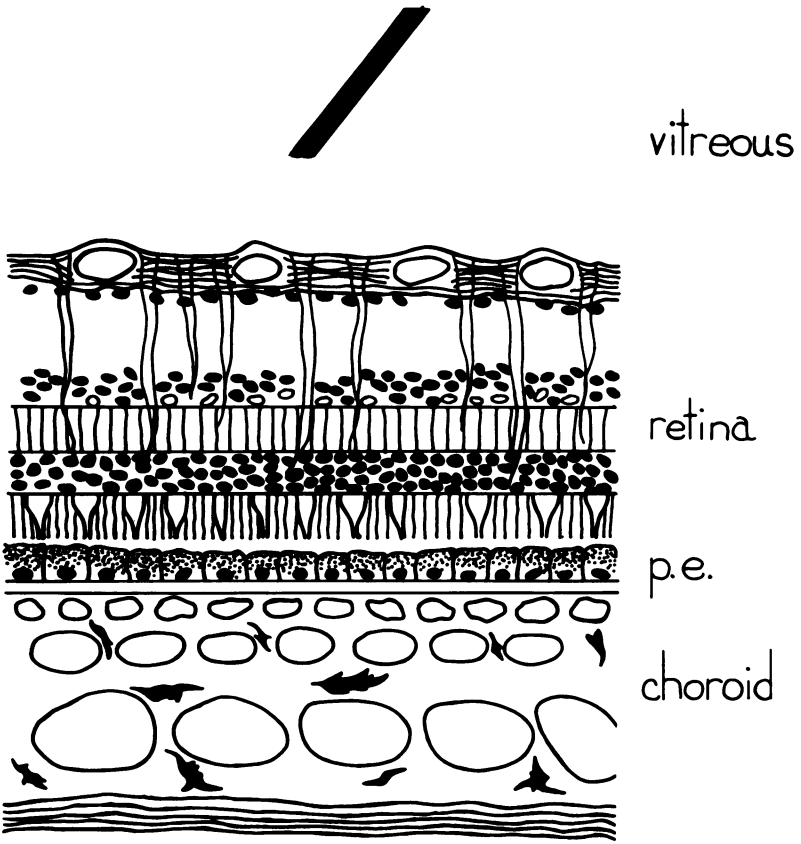


FIGURE 3
Schematic drawing of the choroid and retina with the oxygen electrode placed in the preretinal vitreous. (p.e. = pigment epithelium) When the animal breathes pure oxygen, an oxygen flux is established from the choroid, through the retina into the vitreous where oxygen electrode is placed. The magnitude of this flux to reach the inner retina depends on the O_2 consumption in the outer retina.

If we assume that the choroidal oxygen tension is constant, while the animal is breathing 100% oxygen, then changes in the preretinal oxygen tension reflect changes in the oxygen consumption of the retina. The oxygen flux from the choroid through the retina depends on the oxygen consumption of the tissue. It also depends upon the retinal thickness, diffusion characteristics[20] and temperature, which we measure or assume are constant during the experiment. If the preretinal oxygen tension increases that means the oxygen flux through the retina is higher and the

consumption in the tissue is lower. If the preretinal oxygen tension goes down then the oxygen flux through the retina is decreased indicating that more oxygen has been consumed in the retina. If the consumption is very high the preretinal PO_2 may fall below the saturation PO_2 for hemoglobin in which case O_2 will be released from hemoglobin in the retinal circulation and further drop in the preretinal PO_2 will be buffered, but still the changes will be qualitatively the same.

C. *Oxygen Measurements*

Oxygen tension measurements were performed six to nine months after the laser treatment. The rhesus monkeys were first anesthetized lightly with ketamine HCl and anesthesia reached and maintained with pentobarbital sodium (Nembutal^R) IV approximately 30 mg/kg. The monkeys rested on a thermopad and rectal temperatures were monitored and maintained close to 37 C. The monkeys were intubated and ventilated artificially (Harvard Apparatus Co, Respirator model 661) and CO_2 tension in expired air was monitored (CO_2 Analyser Godart Statham NV, Holland) and kept between 3.5 % and 4.5%. Heart rates were monitored, and intraocular pressures were measured with a Schiøtz indentation tonometer.

The animals' heads were held securely by ear bars. Phenylephrine 5% and tropicamide 0.25% were used to dilate the pupil, and the fundus observed with a Zeiss operating microscope through a flat contact lens placed on the cornea. Lateral canthotomies were performed, sclera exposed and an oxygen electrode inserted through a cannula through the pars plana with the help of a micromanipulator. The oxygen electrode was allowed to stabilize in the vitreous and then advanced until it touched the internal limiting membrane of the retina (evidenced by changes in the light reflection) and withdrawn 0.1 mm and PO_2 measured. The breathing mixture was then changed from room air to 100% oxygen (at atmospheric pressure). Measurements were made over normal and photocoagulated areas of the retina.

The oxygen tensions of the preretinal vitreous were measured over normal and photocoagulated retina with the retinal circulation open and the animal breathing pure oxygen. The method of measuring oxygen tension is similar to that used by other investigators[11,21,23] and consists of a chemical microsensor (model 1201, Transidyne Gen Corp) and a 110 μ platinum (70%) iridium (30%) bare end oxygen electrode mounted inside a 20 gauge steel cannula. An Ag-AgCl reference electrode was placed under the contralateral eyelid during the experiments and placed in the calibration cell for calibration (reference electrode 1251 and calibration cell model 1251, Transidyne General Corporation, Ann Arbor,

Michigan). Standard oxygen tension measuring techniques were followed and the system calibrated in saline at 37 C in 0.0%, 5.0%, and 20.0% oxygen before and after each experiment.[24]

D. *Light Levels*

Ambient light levels were measured with a thermopile. The ambient light level supplied by ordinary fluorescent lights was 55 $\mu W/cm^2$ when the infrared part of the spectrum was filtered out.

E. *Histology*

Following the oxygen measurements the eyes were enucleated and fixed in either 10% formalin or in 4% glutaraldehyde in cacodylate buffer. In some cases the cornea was removed to allow more rapid fixation of the retina. The eyes were embedded in paraplast, sectioned and stained with hematoxylin and eosin and examined with light microscopy.

VITRECTOMY, LENSECTOMY

A. *Surgery*

Domestic cats, 3-5 kg, either sex, were used. The cats were anesthetized with 30-50 mg/kg Ketamine HCl IM and atropine sulfate 0.05 mg/kg. Lensectomy was performed by phacoemulsification. A lateral canthotomy was performed, the conjunctiva cut to expose the sclera and an incision made approximately 6 mm behind the limbus. The phacoemulsification probe was introduced into the eye and the lens emulsified and washed out through the incision. The irrigation fluid was lactated Ringer's solution containing 40 mg gentamycin per liter. Subsequently, the Visc X probe (Clinitex, Varian, Mass) was introduced through the pars plana region and the lens capsule and the vitreous removed. The scleral incision was closed with 7-0 Dexon® as was the conjunctiva, and the canthotomy was closed with 5-0 Dermalon®. Gentamycin, 20 mg was administered subconjunctivally. The eyes were covered with an antibiotic ointment after surgery.

In some cases a diathermy probe was used to occlude retinal veins. It was introduced through the pars plana incision at the beginning of the operation. The three major retinal veins and some of the smaller ones were occluded (the cat has a variable number of cilioretinal veins emerging from the optic disc borders). Each vein was occluded in 2-4 places and a good occlusion was always achieved (Fig 4). However, some of the occlusions recanalized and at the time of the oxygen tension measurement the eyes had only one or two major veins occluded.

B. *Oxygen Measurements*

The oxygen tension measurements were performed one to nine months post-operatively (most were performed six months after the operation.) At

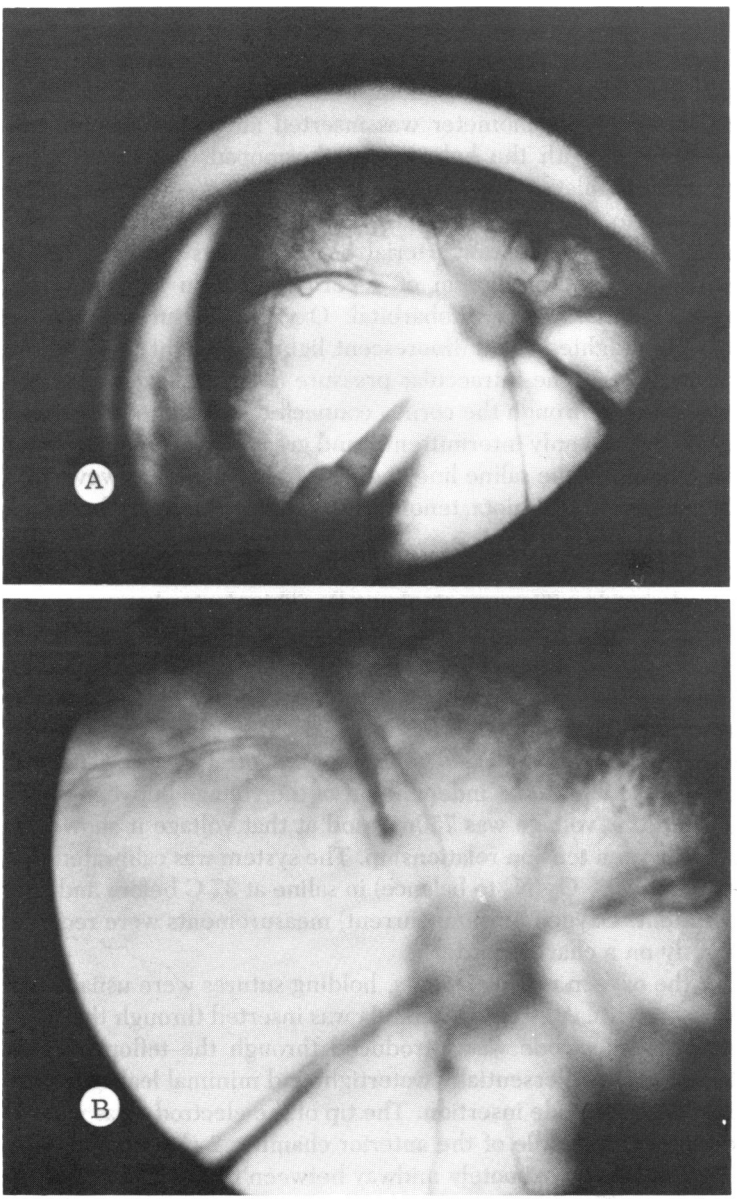


FIGURE 4
Retinal veins in some cats were occluded with a diathermy probe introduced through a pars plana incision. A: diathermy probe can be seen in the vitreous. B: Retinal vessels have been occluded in the cat and the blood flow interrupted.

that time, the cats were again anesthetized with ketamine and atropine IM and anesthesia was maintained with pentobarbital 30 mg/kg IV. Expired air CO_2 tension was monitored and maintained at 3.5%-4.5%. A rectal mercury thermometer was inserted and body temperature kept close to 38 C with the help of the thermopad. A femoral artery was exposed, cannulated and connected to a saline column or a pressure transducer to allow measurements of arterial blood pressure. The same cannula was used to draw arterial blood samples for PaO_2 and $PaCO_2$ measurements. Cannulation of a peripheral vein allowed infusion of Ringer's solution and pentobarbital. Oxygen measurements were performed in a lighted room (fluorescent lights, see light levels above).

In some cases the intraocular pressure (IOP) was measured with a 25 gauge cannula through the cornea connected to a saline manometer. The line was opened only intermittently and great care taken not to allow fluid change between the saline line and eye. In most cases however, IOP was measured with a Schiøtz tenometer without a cannula being inserted through the cornea.

The oxygen meter consisted of a 110 μ platinum-iridium bare wire electrode inside a 20 gauge steel needle. This electrode consumes oxygen at the rate of a few picoliters O_2/min when in the anterior chamber (Zander[60] found the transport rate of O_2 in the anterior chamber to be 0.14 μl 0_2/min). It is connected to a currentmeter (Chemical Microsensor 1201, Transidyne Gen Corp, Mich) and an Ag-AgCl reference electrode which is put under the contralateral eyelid. The electrode current was found to be independent of the voltage between the electrodes when this voltage was 750mV and at that voltage it showed a linear current/oxygen tension relationship. The system was calibrated in 20.0%, 5.0%, and 0.0% O_2 (N_2 to balance) in saline at 37 C before and after each experiment. Oxygen tension (current) measurements were recorded continuously on a chart recorder.

For the oxygen measurements, holding sutures were usually placed in the conjunctiva. A 20 gauge cannula was inserted through the cornea and the oxygen electrode was introduced through the teflon cannula. The entrance port was essentially watertight and minimal leakage occurred at the time of electrode insertion. The tip of the electrode was placed in the midline in the middle of the anterior chamber 2 mm in front of the iris plane (Fig 5), approximately midway between the pupil and the center of the cornea. The baseline oxygen tension in the aqueous humor was recorded for at least two hours. Anterior chamber oxygen tension was measured in three groups (A) intact cat eyes; (B) cat eyes, which had had the vitreous and lens removed months earlier; (C) cat eyes, which had had

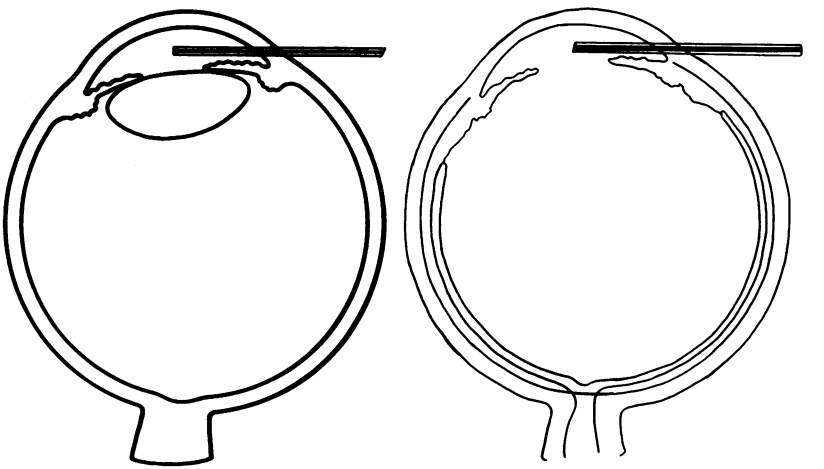


FIGURE 5
A: Schematic drawing of the oxygen electrode in the middle of the anterior chamber of the otherwise intact eye. B: Schematic drawing of the oxygen electrode in the middle of the anterior chamber of the vitrectomized, lensectomized eye.

the vitreous and lens removed and some of the retinal veins occluded, a few months earlier.

In two vitrectomized/lensectomized eyes and one normal eye a probe was introduced through the pars plana to press on the optic disc and occlude the retinal blood flow,[3] while the anterior chamber PO_2 was being measured.

RESULTS

PHOTOCOAGULATION STUDY

In all eight rhesus monkey eyes a definite difference in oxygen tension was found between the normal and the photocoagulated areas of the retina, when the monkey was breathing 100% O_2 (Fig 6, Table V). The average difference in PO_2 between the photocoagulated and normal areas of the same retina was 41.0 ± 15.0 mm Hg, the PO_2 being higher over the photocoagulated areas than over the normal areas of the retina.

No significant difference was found between the treated and normal areas when the animal was breathing room air (Table IV). The oxygen tension over the normal retina was 8.6 ± 4.5 mm Hg and 10.0 ± 2.5 mm Hg over the photocoagulated retina. Table VI lists the average and standard deviations of body temperature, CO_2% in expired air, heart rate and intraocular pressure. The appearance of the laser lesions in the rhesus

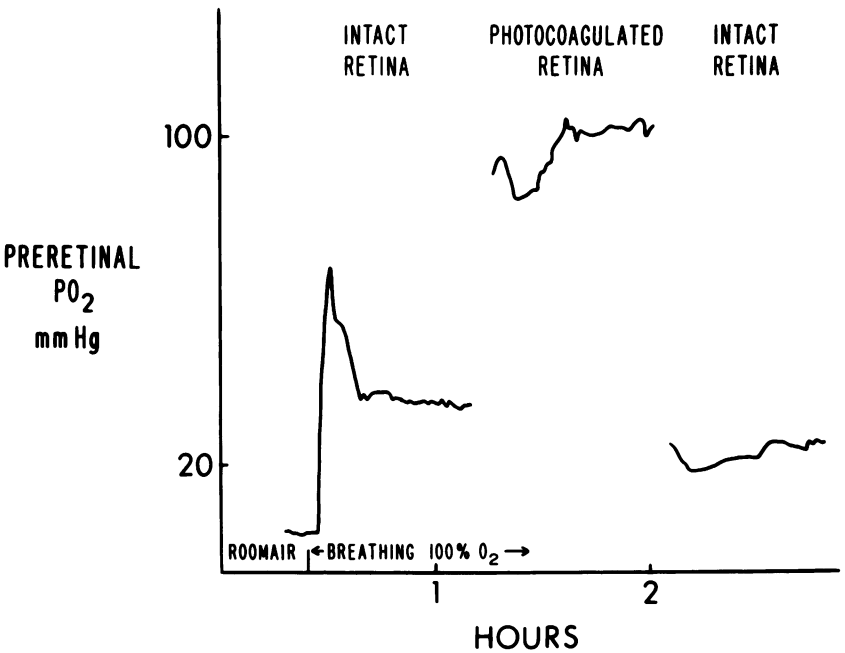


FIGURE 6

Ordinate: Preretinal oxygen tension (mm Hg). Abscissa: Time (hours). This graph demonstrates the difference in preretinal oxygen tension between the intact areas and the photocoagulated areas of the same retina. The rhesus monkey was first breathing room air and then breathing pure oxygen at one atmosphere pressure for the rest of the experiment as indicated on the graph. The preretinal oxygen tension was measured 2 to 3 disc diameters from the disc in superior fundus which has been photocoagulated and inferior fundus which was intact.

monkeys were very similar to the lesions seen after panretinal photocoagulation in patients (Fig 1B).

Light microscopy showed that the laser burn lesions were confined to the outer retina ie, the photoreceptor layer and the pigment epithelium, whereas the inner retina was left intact (Fig 1C and D).

VITRECTOMY-LENSECTOMY STUDY

Measurements showed a significant difference between the intact eyes and the two other groups (Fig 7) in spite of some variance within each group (Fig 8). The normal oxygen tension in the anterior chamber of the intact cat eye was 34.0 ± 6.8 mm Hg (12 eyes). This is different (99.5% confidence) from the six cat vitrectomy-lensectomy eyes, which had an

TABLE IV: ARTERIAL BLOOD PRESSURE, ARTERIAL OXYGEN TENSION, INTRAOCULAR PRESSURE, PERCENTAGE OF CO_2 IN EXPIRED AIR AND BODY TEMPERATURE OF THE CATS DURING THE EXPERIMENTS. AVERAGE, STANDARD DEVIATION AND RANGE ARE GIVEN.

	ALL EYES	NORMAL EYES	VITRECTOMIZED LENTECTOMIZED EYES	VITRECTOMIZED, LENTECTOMIZED EYES WITH RETINAL VEIN OCCLUSION
Arterial Blood Pressure mm Hg	125.2 ± 29.8	136.5 ± 12.2	116.9 ± 37.4	121.3 ± 31.4
Arterial Oxygenation P_aO_2 (hg)	97.6 ± 16.5 (62 – 126)	100.5 ± 18.3 (82 – 126)	91.4 ± 17.0 (62 – 104)	93.3 ± 9.1 (85 – 103)
Intraocular Pressure (IOP) mm Hg	8.3 ± 6.1 (4 – 22)	8.6 ± 6.2 (4 – 21)	10.2 ± 7.2 (4 – 22)	4.0 ± 0.0 (4)
Percentage CO_2 In Expired Air*	3.9 ± 0.4 (3.0 – 4.5)	4.0 ± 0.4 (3.0 – 4.5)	3.7 ± 0.5 (3.0 – 4.3)	3.5 ± 0.2 (3.3 – 3.6)
Body Temperature °C	36.9 ± 1.7 (33.0 – 39.5)	37.4 ± 1.6 (34.0 – 39.5)	36.2 ± 2.1 (33 – 38)	37.0 ± 0.0 (37)

*at sea level

TABLE V: PRERETINAL OXYGEN TENSION IN RHESUS MONKEYS

	BREATHING ROOM AIR	BREATHING PURE O_2 AT 1 ATM
Normal Retina	8.6 ± 4.5 (n = 5)	86.2 ± 41.1 (n = 8)
Photocoagulated retina	10.0 ± 2.5 (n = 6)	127.3 ± 39.4 (n = 8)
Difference between the normal and photocoagulated areas of the same retina	2.3 ± 1.1 (n = 3)	41.0 ± 15.0 (n = 8)

oxygen tension of 22.2 ± 5.9 mm Hg in the anterior chamber and also from the three cats' eyes which had undergone vitrectomy, lensectomy and (partial) retinal vein occlusion, and which had an oxygen tension of 16.7 ± 4.0 mm Hg in the aqueous humor in the anterior chamber.

Occlusion of the retinal circulation by pressing a probe on the optic disc resulted in a drop in the anterior chamber PO_2 in the two vitrectomized lensectomized eyes (Fig 9), but not in the one normal eye.

Arterial blood pressure, arterial blood oxygen tension, expired CO_2 tension, body temperature and intraocular pressure were similar in all groups (Table IV).

DISCUSSION

Panretinal photocoagulation has been shown to be a useful treatment in proliferative retinopathy due to diabetes[25,32] and venostasis retinopathy.[33,36] The laser treatment destroys some of the photoreceptors and

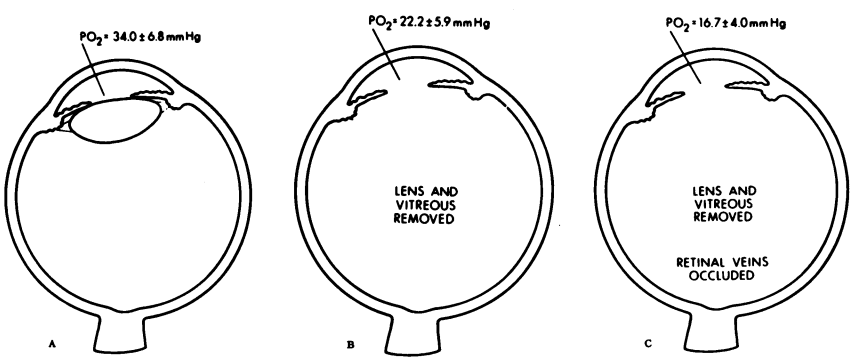


FIGURE 7

Schematic drawings of the experimental eyes with the oxygen tension levels in the aqueous humor in the anterior chamber indicated. A: Intact eyes (n = 12). B: Vitrectomized, lensectomized eyes (n = 6). C: Vitrectomized, lensectomized eyes with the retinal veins occluded (n = 3).

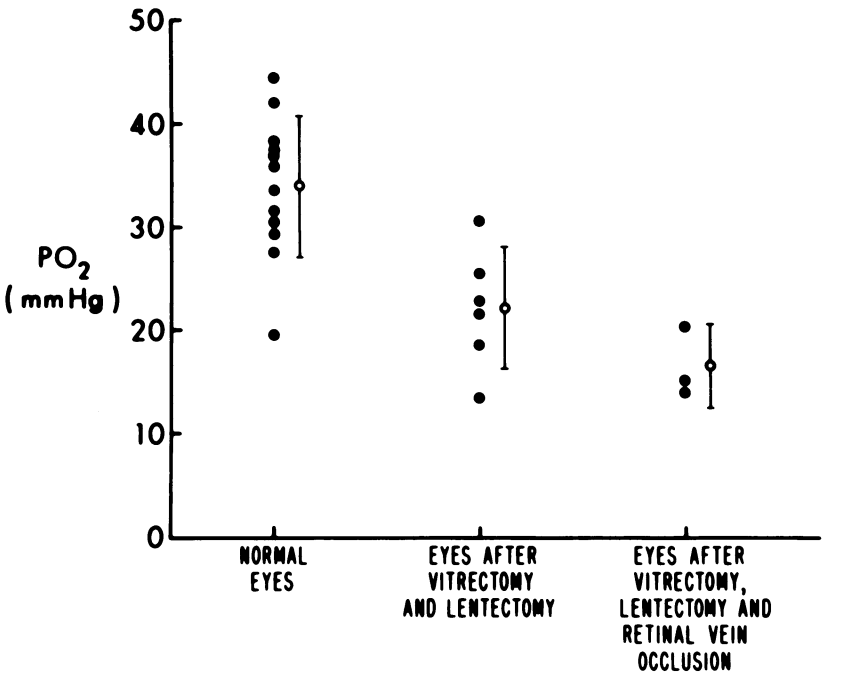


FIGURE 8
Graph shows oxygen tension in aqueous humor in the anterior chamber in three groups of cat eyes and the mean and standard deviation in each group. Each dot is the PO_2 in one eye.

decreases the oxygen consumption of the outer retina and allows oxygen to diffuse to the inner retina from the choroidal circulation thus relieving the hypoxia thought to stimulate new vessel growth.[1,2] The histologic changes seen after photocoagulation consist of damage to the outer retina and the pigment epithelium whereas the inner retina is spared in low and medium intensity argon laser treatment.[23,37-45] Laser treatment of the retina can also affect the choriocapillaris but this study shows that this has insignificant effects on blood flow and oxygenation as the choroidal oxygen flux to the inner retina is increased in the photocoagulated areas.

In retinal laser treatment, most of the photoenergy is absorbed by the pigment epithelium and conducted to the photoreceptors and these are the only layers damaged in low energy photocoagulation as used in the present study. As the energy is increased the burn will become more extensive and eventually involve the whole thickness of the retina.[23,47,48] Powell et al[38] showed that 7.5 mJ from an argon laser on a 50 μ

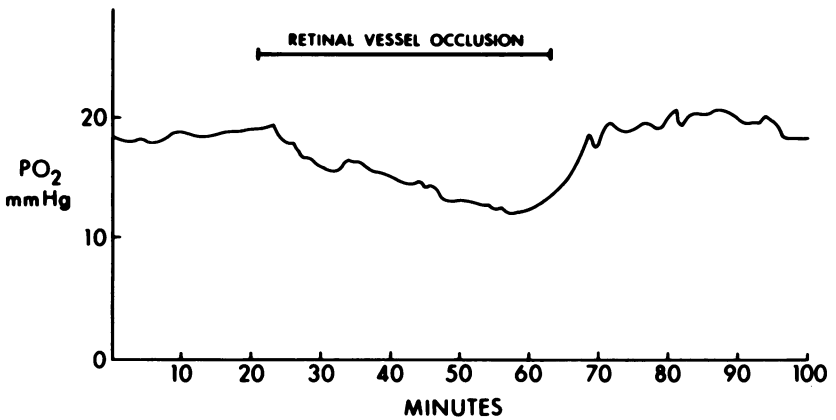


FIGURE 9
Oxygen tension in anterior chamber of a vitrectomized/lensectomized eye. Retinal circulation was occluded by pressing a probe on the optic disc and the fall in anterior chamber oxygen tension observed. Oxygen tension reversed to baseline value when retinal circulation was re-opened. Abscissa: Oxygen tension in aqueous humor in the anterior chambers of the cat eyes (mm Hg). Ordinate: Time (minutes).

diameter spot did not affect the inner retina in rhesus monkeys and 18.8 mJ (150 mW for 125 msec) destroyed the outer retina but only reached the outer part of the inner nuclear layer. Landers et al[46] found that 12 mJ (60 mW for 0.2 sec) on a 100 μ spot only burned the outer retina in a human patient. Wallow et al[48] found that 250-400 mJ xenon arc burns (500-800 mW for 0.5 sec) on a 500 μ spot produced damage to the inner retina and outer retina in humans. Diddie and Ernest[23] found that 0.1 W for 0.2 sec on 1000 μ spots only damaged the outer retina of rhesus monkeys leaving the inner retina intact. When the argon laser power was raised to 1.0 W (0.2 sec, 1000 μ spot) a full thickness burn was produced. Low energy photocoagulation, such as used in this study and used to treat patients in our clinic, damages and outer retina and the pigment epithelium and leaves the inner retina and the chorio-capillaris almost intact. If more powerful laser treatment is used, it will cause a more extensive lesion. The photoreceptors contain most of the mitochondria of the retina and reducing their number will markedly decrease the total oxygen consumption of the retina.[49,50]

The laser treatment carried out in this study only damaged the outer retina, ie, the photoreceptor layer and the pigment epithelium, and this simulates effective clinical laser treatment of diabetics in this clinic. The result of this treatment is a markedly increased oxygen flux across the

TABLE VI: BODY TEMPERATURE, HEART RATE, INTRAOCULAR PRESSURE AND CO_2 TENSION IN EXPIRED AIR IN THE RHESUS MONKEYS DURING OXYGEN MEASUREMENTS. AVERAGE AND STANDARD DEVIATION IS GIVEN.

Temperature	36.0 ± 0.8 C
Heart rate	134 ± 14 min^{-1}
Intraocular Pressure	9.8 ± 3.6 mm Hg
CO_2 in expired air	3.7 ± 0.4%

retina as a result of the decreased O_2 consumption in the outer retina. The oxygen flux from the choroid to the inner retina is increased in the photocoagulated retina as less oxygen is consumed in the partially burned outer retina.

Fick's laws of diffusion[20] predict that the decrease in oxygen tension across the retina is a linear function of the oxygen consumption in the tissue when the input of the retinal circulation is nullified. This applies to the normal situation and when the animal breathes pure O_2, but in the normal situation when the animal breathes room air the retinal circulation regulates the inner retinal PO_2 by changing its own flow and the choroidal input cannot easily be measured.

The choroidal oxygen flux in the photocoagulated retina serves to decrease the demand on the retinal circulation, which responds to this new source of oxygen by constricting and decreasing its blood flow.[31,51] The autoregulation of the retinal circulation will decrease the retinal blood flow if the oxygen flux from the choroid is increased.[19] If the choroidal oxygen flux is within the autoregulatory capacity of the retinal circulation, no change will be seen in inner retinal PO_2. This explains why we found no significant difference in the oxygen tension between the normal and photocoagulated areas, when the monkeys were breathing room air.

Diddie and Ernest[23] also found no difference in PO_2 between normal and photocoagulated retina in animals breathing room air. In animals breathing room air the changes in the choroidal oxygen flux are small enough for the retinal circulation to completely compensate for it and keep the retinal PO_2 constant in spite of the differences in the choroidal oxygen flux. Only when the choroidal oxygen flux is increased and the autoregulatory capacity of the retinal circulation decreased by the animal breathing pure O_2 is the choroidal oxygen flux increased beyond the autoregulatory capacity of the retinal circulation and a difference in inner retinal PO_2 detectable.

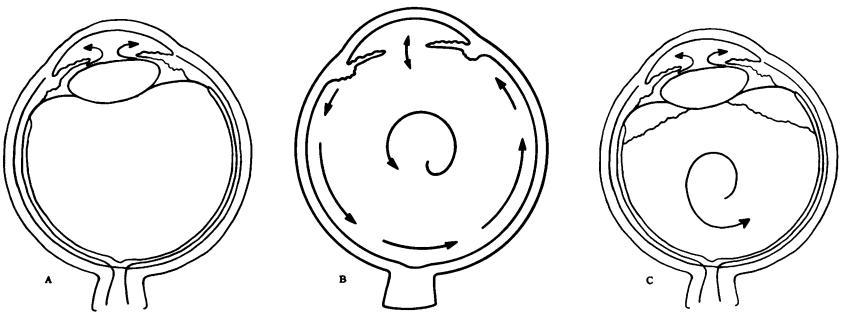


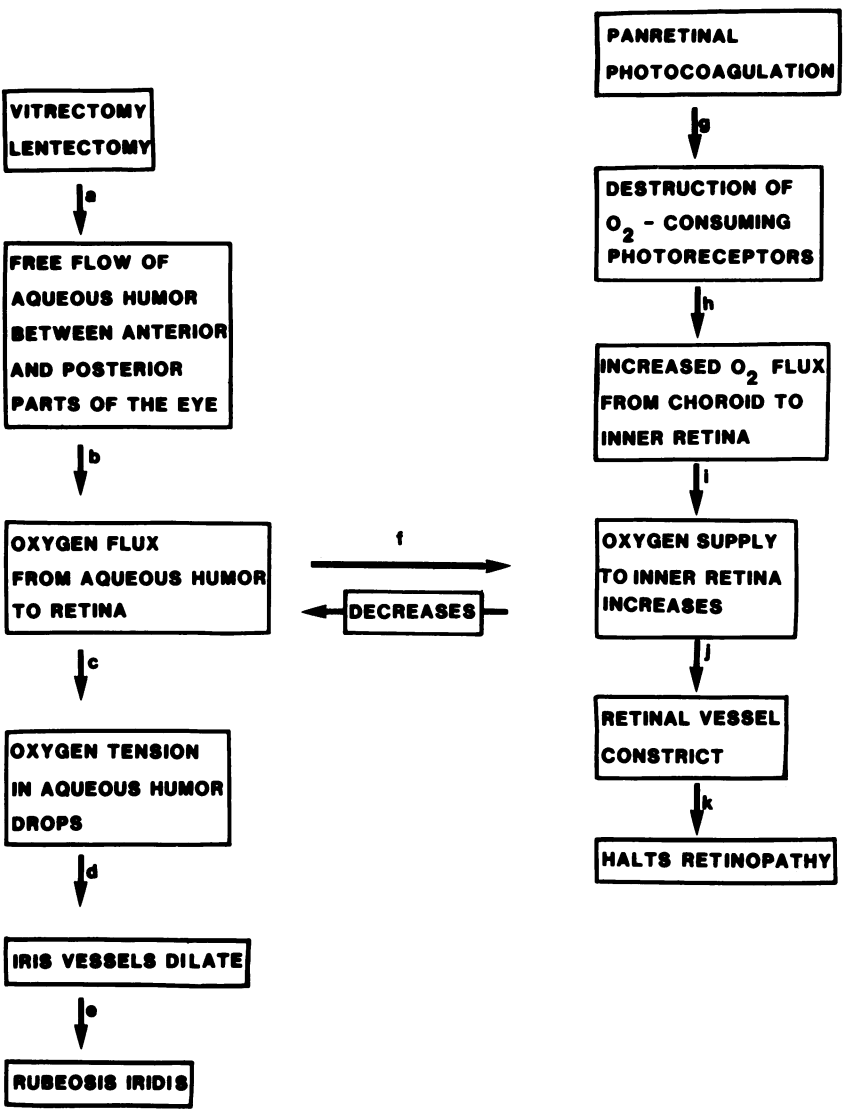
FIGURE 10
Schematic drawing to indicate the fluid flow in the eye. A: In the intact eye. B: In an eye after vitrectomy and lensectomy (free flow back and forth). C: After vitrectomy when lens was left in place.

The introduction of a new source of oxygen to the inner retina and the effect this has on the retinal circulation may be critical to the management of diabetic retinopathy.[1] As we have shown this can be done by panretinal photocoagulation making oxygen available from the choroidal circulation. The inner retina can also receive extra oxygen from the aqueous humor if the vitreous and lens are removed and the relatively oxygen rich aqueous bathes the inner surface of the retina.

The inner retina in cats and monkeys has an oxygen tension of about 20 mm Hg or less[11,21,23,52,54] whereas the aqueous humor in the anterior chamber normally has PO_2 above 30 mm Hg.[55-59] The lens and vitreous normally prevent the bulk flow of aqueous humor to the retinal surface (Fig 10). Transport of oxygen by diffusion through the vitreous is too slow to eliminate the difference in PO_2 between the anterior chamber and the inner retina.

If the aqueous humor bathes the retina as it does after vitrectomy and lensectomy, the oxygen tension of the aqueous will fall close to the retinal PO_2 as O_2 diffuses from the aqueous into the retina.

When the vitreous and lens are removed, the eye is filled with fluid which will move freely throughout the eye and rapidly carry oxygen and other solutes from one part of the eye to another (Fig 10). In this "one chamber eye" we have found the oxygen tension to be nearly equal in the fluid in the front and the back of the eye. Since the retina consumes much oxygen and covers more than half the surface of the "chamber," the retina can markedly affect the PO_2 in this fluid. It is, therefore, no surprise to find the PO_2 in the aqueous humor in anterior chamber in the vitrectomized and lensectomized cat eye to be similar to the normal pre-


VITRECTOMY
LENTECTOMY
a
FREE FLOW OF AQUEOUS HUMOR BETWEEN ANTERIOR AND POSTERIOR PARTS OF THE EYE
b
OXYGEN FLUX FROM AQUEOUS HUMOR TO RETINA
c
OXYGEN TENSION IN AQUEOUS HUMOR DROPS
d
IRIS VESSELS DILATE
e
RUBEOSIS IRIDIS
f
DECREASES
PANRETINAL PHOTOCOAGULATION
g
DESTRUCTION OF O_2 - CONSUMING PHOTORECEPTORS
h
INCREASED O_2 FLUX FROM CHOROID TO INNER RETINA
i
OXYGEN SUPPLY TO INNER RETINA INCREASES
j
RETINAL VESSEL CONSTRICT
k
HALTS RETINOPATHY

retinal PO_2, and also to see the further decrease in anterior chamber PO_2 when the retina is made ischemic (Fig 9).

The present study suggests that the drop in anterior chamber aqueous oxygen tension after vitrectomy and lensectomy may be due to the oxygen uptake by the retina. If the retina is rendered hypoxic through a partial retinal vein occlusion in the vitrectomized/lensectomized eye, the oxygen flux to the retina is increased resulting in the aqueous PO_2 falling even more. The aqueous is more likely reoxygenated[60] to some extent as it flows along well oxygenated areas in the eye, such as the ciliary body, and may even receive oxygen from well perfused areas of the retina and release oxygen mainly to the poorly perfused, hypoxic areas of the retina. Vitrectomy and lensectomy introduces a new source of oxygen to the inner retina. Inner retinal oxygen tension can also be improved by panretinal photocoagulation. *The effect of both* of these treatment modalities, ie, panretinal photocoagulation and vitrectomy/lensectomy, is to improve inner retinal oxygenation (Fig 10). Both seem to inhibit the progress of proliferative diabetic retinopathy.[26,61]

A model explaining the effect of vitrectomy/lensectomy and panretinal photocoagulation on improving the oxygenation of the inner retina is summarized in Figure 11. This explanation ties in closely with our model of the pathogenesis of proliferative diabetic retinopathy,[1] and also can be understood in light of other models for the pathogenesis of proliferative diabetic retinopathy.[2]

FIGURE 11

Flow diagram to explain effect of panretinal photocoagulation and vitrectomy/lensectomy on oxygenation in the eye and how this may relate to neovascularization of iris and retina. EXPLANATION OF ARROWS: a. Vitrectomy and lensectomy remove a physical barrier to fluid flow to back of the eye (Fig 10). b. Relatively oxygen rich aqueous humor gives oxygen to retina, and more so if retina is made hypoxic (Fig 7,8,9). c. See Figure 7,8,9. d. Hypoxia causes dilatation of the iris vessels in the cat and increased iris blood flow.[79] We have confirmed this in the albino guinea pig. e. This step is hypothetical.[1] However iris vessel dilatation has been described as a precursor of rubeosis iridis in people.[80] f. An oxygen flux from aqueous humor to the retina constitutes a new source of oxygen to the inner retina. On the other hand, if the retina receives oxygen from other sources to increase its PO_2, then oxygen uptake from the aqueous humor will decrease. g. Laser treatment of low energy (as used to treat patients in this clinic) only damages the outer retina. The photoreceptors contain most of the mitochondria in the retina and consume much of the O_2 used by the retina. h. By decreasing O_2 consumption in outer retina, more O_2 can diffuse through and reach inner retina (Fig 6, Table V). i. New supply of oxygen to the inner retina comes from the choroid in the case of panretinal photocoagulation. j. Retinal vessels autoregulate their blood flow to compensate for changes in oxygen supply.[18,19] They will constrict in response to a new source of oxygen. This has been demonstrated following vitrectomy and lensectomy (Dr McCuen, personal communication 1981). k. Hypothetical step.[1] Panretinal photocoagulation and vitrectomy lensectomy do halt the progress of retinopathy. We have proposed a mechanism,[1] which remains unproven.

SUMMARY

Panretinal photocoagulation as well as vitrectomy are the main treatment modalities for diabetic and other proliferative retinopathies. We show that both treatments introduce a new source of oxygen to the inner retina and propose that their efficacy in controllng the retinopathy results from their effect on the oxygenation of the inner retina.

Panretinal photocoagulation reduces the oxygen consumption of the outer retina and allows more oxygen to diffuse to the inner retina from the choroid. Vitrectomy/lensectomy on the other hand allows aqueous humor to flow back to the retina and give oxygen to the inner retina which normally has a lower PO_2 than aqueous humor. This causes the PO_2 in aqueous humor to fall.

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DISCUSSION

DR J. TERRY ERNEST. Professor Norman Ashton has made the comment that the era of the histological study of diabetic retinopathy is over and that we are now ready to study the physiology of the disease process. The authors are to be congratulated for giving us physiologic data with a view towards the further understanding of diabetic retinopathy and its treatment. They have taken on a formidable task to explain the pathophysiology of diabetic retinopathy, to explain how photocoagulation works and to explain how lensectomy and vitrectomy work. In order to understand better the authors' contribution we should look carefully at what is known about the ocular circulation.

The retinal blood flow is approximately the same as brain white matter but the tissue oxygen tension is only about half. The latter may make the retina especially susceptible to hypoxia. There is no autonomic innervation and the circulation autoregulates. The autoregulatory capacity of the retinal circulation appears to be compromised in early diabetic retinopathy. The choroidal circulation has the highest blood flow per gram of tissue in the body. There is an autonomic nervous supply and a sympathetic tonus. Indeed, destruction of the sympathetic innervation to the choroidal vasculature may result in "leaky" disease. The cho-

roidal circulation does not autoregulate but may be controlled by the amount of light generated heat of the retina.

Armed with this information, there are two aspects of the authors' work I would like to comment on. First, having increased oxygen is not necessarily good, that is to say, in diabetics we are concerned about decreased perfusion with capillary drop out, and the constriction of blood vessels may be detrimental in itself. I'm sure the authors would not recommend, for instance, treatment of diabetic retinopathy with 100% oxygen inhalation. Second, the authors have shown that following photocoagulation, the breathing of 100% oxygen results in an increase of retinal oxygen tension far above normal, and they conclude that this is because the retina consumes less. But we know that the choriocapillaris is also destroyed by the burns and thus another interpretation might be that photocoagulation actually interrupts autoregulation, and the circulation can no longer adapt to 100% oxygen inhalation. I present this possibility not because I am sure this is so but because it is another interpretation of the authors' data, and indeed, there may be several other interpretations that neither of us has thought of.

This does not diminish the tremendous job the authors have done to make the measurements of ocular oxygen tension, and I believe their contribution to be most important for our understanding of the pathophysiology of diabetic retinopathy and its treatment.

DR A. RODMAN IRVINE. I just can't help saying something here, as I think this is so pertinent to the major thesis that Doctor Landers is presenting. In essence, he is saying that the vasoproliferative factors that we've been trying to build models to study may be like the "Emperor's New Clothes." They may not exist. In discussing our monkey model of radiation induced chronic ischemic retinopathy, we talked about taking out the lens and the vitreous to promote rubeosis irides, and then studying the vasoproliferative factors involved. Doctor Landers is saying that instead of some unknown vasoproliferative factor going forward from the retina to cause the rubeosis irides, what's happening is simply that when you've taken out the lens and the vitreous, the retina is stealing the oxygen from the anterior segment. I've been trying to think how we could test these two theories, which each give the same end point but in a very different manner. I would like to ask Doctor Landers a question, knowing that he has done a lot of work with increased ambient O_2. If we can get our model to the point where we find that we can make the retina ischemic and then do a lensectomy and vitrectomy and produce rubeosis irides, would it be feasible to raise the oxygen tension in the anterior chamber back up to the normal levels you were talking about by simply keeping these animals in a relatively high oxygen environment? Would it be feasible to do this in order to determine whether hypoxia is the cause of the rubeosis rather than some chemical factor coming forward from the ischemic retina?

DR MAURICE B. LANDERS. I would like to thank Doctor Ernest for his comments. I think everyone knows he has studied oxygen tension in the eye and is probably

more knowledgable about it than anyone else in the country. He and I will perhaps discuss in the future just what mechanisms are involved here and I do think it would be productive to do that. As far as Doctor Irvine's comments, I think his suggestion is a fascinating one. We have had the opportunity to produce rubeosis of the iris in cats using this model which we presented at the most recent ARVO meeting. I certainly think it would be interesting to change the oxygen environment. I think one needs to be very careful in drawing any conclusions here. We're working in experimental situations which clearly don't precisely mimic the diseases that we wish to study and it may be that we draw one set of conclusions from the experiment which really don't relate to the disease. In other words, I am very interested in this and excited not only by the things that we seem to be finding but I think only by these mechanisms are we ever going to have any idea just what it is we are doing when we carry out these devastating treatments of diabetic retinopathy and take out the vitreous. So I think it's going to take more work on models such as these but with very careful interpretation of what one has actually done.